REMARKS

Upon entry of the present amendment, claims 2, 3, 12, 32 and 37 have been amended, and claims 2-8, 12, 14, 24 and 32-50 are pending. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made".

Claim Rejections - 35 USC 112

1. New Matter: Applicant respectfully submits that the provisos for G in the present claims are fully supported by the specification.

As now claimed, (independent claims 1 and 12), G is not $-(CH_2)_n-(CR^{14}R^{15})_s-R^{13}$ when other indicated substituents are defined as indicated. Support for this negative limition is at page 20, line 17 to page 21 line 3 of the specification.

Further as claimed, G is not phenyl, N-containing heteroaryl or $(-CH_2)_{ma}-CHR^{10a}R^{11a}$, when other indicated substituents are defined as indicated (independent claims 2, 3, 12 and 32). Support for this limitation is in the specification starting at line 13 on page 2 of the specification, compounds described in EP0210782 "are excluded from the present claimed scope of protection according to the invention." Compounds where G is phenyl, N-containing heteroaryl or $(-CH_2)_{ma}-CHR^{10a}R^{11a}$ are described in the '782 patent and are properly excluded.

2. New Matter: Applicant respectfully submits that claims 35-39 are fully supported by the present invention. Support for each of the claims is as follows.

Claim 35: At page 97, lines 16-29 of the specification indicates that compound of formula (I) can be produced by reacting compounds of formula (I) when G is hydrogen with L-G(IV). Accordingly, one of the reactants in claim 35 is formula (I) where G is hydrogen.

Claim 36: At page 97, line 29-33, the specification indicates that compounds of formula (I) where G = G^1 can be synthesized by reacting compounds of formula (I) where G is hydrogen with L-G (IV).

Claim 37: Claim 37 has been amended to make it the same as page 98, line 34 to page 99, line 17. As indicated in the specification, compounds of formula (I) can be made by reacting compounds of formula (I) where G is hydrogen with HO-G(V).

Claim 38: At page 99, line 22 to line 26, the specification indicates that compounds of formula (I) can be produced by reacting compounds of formula (I) where G is hydrogen with $H\text{-}NR^{13}R^{15}$(VI).

Claim 39: At page 101, lines 11 to line 14, the specification indicates that compounds of formula (I) can be produced by reacting compounds of formula (I) where G is hydrogen with $O{=}C{=}N{=}R^{13}$ (VII).

3. Scope of Enablement: Applicant respectfully submits that claims directed to method of inhibiting tumor cell growth (claim 33) and a method of suppressing and autoimmune disease (claim 34) are fully enabled by the specification.

As to methods of inhibiting tumor cell growth, the specification provides the following specific examples.

Page 166, Example 2, and page 170 (Table) describe inhibiting growth of tumor lung carcinoma.

Page 167, Example 3, and page 170 (Table) describe inhibiting growth of colon carcinoma.

Page 168, Example 4, and page 170 (Table) describe inhibiting monocytic leukemia.

Page 170 (Table) describes inhibiting hepatocellular carcenoma.

In addition, the specification indicates at page 169, lines 20-30, the compounds of the invention are effective for use in treating "gynaecological tumors, ovarian carcinomas, testicle tumors, prostate carcinomas, skin cancer, kidney cancer, bladder tumors, oesophagus carcinomas, stomach cancer, rectal carcinomas, pancreas carcinomas, thyroid cancer, adrenal tumors, leukemia and lymphomas, Hodgkin's disease, tumor illnesses of the CNS, soft-tissue sarcomas, bone sarcomas, benign and malignant mesotheliomas, but especially intestine cancer, liver cancer, breast cancer, bronchial and lung carcinomas, melanomas, acute and chronic leukemias. Benign papillomatosis tumors can also be limited in their growth with the named substances."

In view of this extensive description of activity, Applicants submit they have done far more than what is required under 35 USC 112 to enable claims to be method of inhibiting tumor cell growth.

As to the method of suppressing autoimmune disease, the specification describes immunosuppressing activity starting at page 171. Applicants respectfully submit that this description provides all that is required under 35 USC 112 to fully enable claims to suppressing autoimmune disease.

Claim Rejections - 35 USC 102

4. Claims have been amended as suggested by the Examiner to exclude compounds were R^{13} and R^{14} are both phenyl groups:

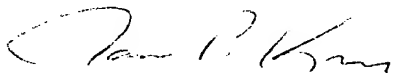
second negative limitation, where G does not represent -$(CH_2)_{ma}$-CHPhPh when other indicated substituents are defined as indicated. Hence, the provisos for G now distinguish all of the cited references.

Conclusions

In view of the above amendments and remarks, applicants respectfully request that the pending claims be passed to issue. The Commissioner is hereby authorized to charge any additional fees which may be required in this application to Deposit Account No. 06-1135.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By 

James P. Krueger
Registration No. 35,234

Date: December 30, 2002
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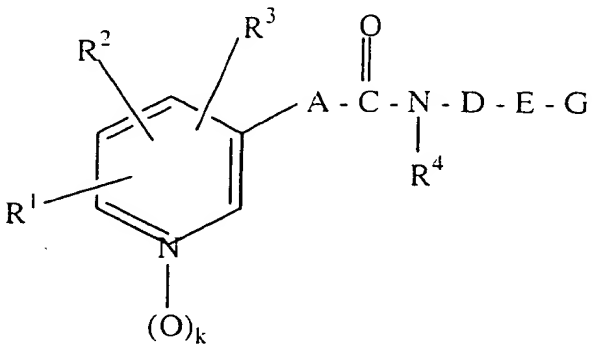
Version to Show Changes Made

2. (twice amended) Pyridylalkane, pyridylalkene and pyridylalkine carboxamindes of formula (I)



(I)

wherein:

R^1 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_2-C_6-alkinyl, trifluoromethyl, C_3-C_8-cycloalkyl, C_1-C_6-hydroxyalkyl, hydroxy, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkinyloxy, benzyloxy, C_1-C_7-alkanoyloxy, C_2-C_7-alkoxycarbonyloxy, C_1-C_6-alkylthio, C_3-C_6-alkenylthio, C_3-C_6-alkinylthio, C_3-C_8-cycloalkyloxy, C_3-C_8-cycloalkylthio, C_2-C_7-alkoxycarbonyl, aminocarbonyl, C_2-C_7-alkylaminocarbonyl, C_3-C_{13}-dialkylaminocarbonyl, carboxy, phenyl, phenoxy, phenylthio, pyridyloxy, pyridylthio, and NR^5R^6, wherein

R^5 and R^6 are selected independently of each other from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, benzyl and phenyl;

R^2 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, hydroxy, C_1-C_6-alkoxy, benzyloxy and C_1-C_7-alkanoyloxy;

R^1 and R^2, if adjacent, may form a bridge selected from $-(CH_2)_4-$ and $-(CH=CH)_2-$ or $CH_2O-CR^7R^8-O-$, wherein R^7 and R^8 are selected independently from each other from hydrogen and C_1-C_6-alkyl;

R^3 is selected from the group consisting of hydrogen, halogen, C_1-C_6-alkyl, trifluoromethyl and C_1-C_6-hydroxyalkyl;

R^4 is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_3-C_6-cycloalkyl, hydroxy, C_1-C_6-alkoxy and benzyloxy;

k is 0 or 1,

A is selected from the group consisting of

C_1-C_6-alkylene,

a substituted C_1-C_6-alkylene which is substituted one to three-fold by C_1-C_3-alkyl, hydroxy, C_1-C_3-alkoxy, fluorine, or phenyl,

C_2-C_6-alkylene, in which a methylene unit is isosterically replaced by O, S, NR^9, CO, SO or SO_2, wherein, with the exception of CO, the isosteric substitution is not adjacent to the amide group and R^9 is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_1-C_6-acyl and C_1-C_6-alkanesulfonyl,

1,2-cyclopropylene,

C_2-C_6-alkenylene,

a substituted C_2-C_6-alkenylene which is substituted once to three-fold by C_1-C_3-alkyl, hydroxy, C_1-C_3-alkoxy, fluorine, cyano or phenyl,

C_4-C_6-alkadienylene,

a substituted C_4-C_6-alkadienylene which is substituted once or twice by C_1-C_3-alkyl, fluorine, cyano or phenyl;

1,3,5-hexatrienylene,

a 1,3,5-hexatrienylene which is substituted by C_1-C_3-alkyl, fluorine, cyano or phenyl, and

ethinylene,

D is selected from the group consisting of C_2-C_{10}-alkylene,

a substituted C_2-C_{10}-alkylene which is substituted once or twice by C_1-C_6-alkyl, hydroxy, or C_1-C_6-alkoxy;

C_4-C_{10}-alkenylene,

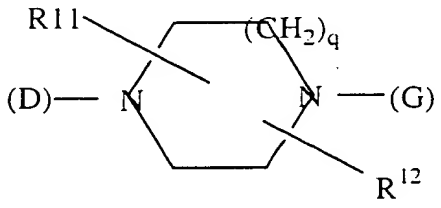
a substituted C_4-C_{10}-alkenylene which is substituted once or twice by C_1-C_6-alkyl, hydroxy, or C_1-C_6-alkoxy;

C_4-C_{10}-alkinylene,

a substituted C_4-C_{10}-alkinylene which is substituted once or twice by C_1-C_6-alkyl, hydroxy, or C_1-C_6-alkoxy; and

C_2-C_{10}-alkylene, C_4-C_{10}-alkenylene or C_4-C_{10}-alkinylene, in which one to three methylene units are isosterically replaced by O, S, NR^{10}, CO, SO, or SO_2, wherein R^{10} has the same meaning as R^9, but is selected independently thereof;

E is



wherein

q is 1, 2, or 3;

R^{11} is selected from the group consisting of hydrogen C_1-C_6-alkyl, hydroxy, hydroxymethyl, carboxy, or C_2-C_7-alkoxycarbonyl,

R^{12} is selected from the group consisting of hydrogen, C_1-C_6-alkyl and an oxo group adjacent to a nitrogen atom,

and wherein R^{11} and R^{12} may together form a C_1-C_3-alkylene bridge under formation of a bicyclic ring system;

G is selected from the group consisting of G1, G2, G3, G4, and G5, wherein

G^1 is $-(CH_2)_r-(CR^{14}R^{15})_s-R^{13}$

r is 0, 1, 2 or 3,

s is 0 or 1,

R^{13} is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_3-C_8-cycloalkyl,

saturated or unsaturated four to eight-membered heterocycles,

saturated or unsaturated four to eight-membered heterocycles which contain one or two hetero-atoms selected from the group consisting of N, S and O,

benzyl, phenyl,

monocyclic aromatic five or six-membered heterocycles which contain one to three hetero-atoms selected from the group consisting of N, S and O where the heterocycles are either bound directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated carbocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein the linkage may occur either over an aromatic or a hydrogenated ring and either directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated heterocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein one to three ring

atoms are selected from the group consisting of N, S and O and the linkage may occur either over an aromatic ring or a hydrogenated ring and either directly or over a methylene group,

R^{14} has the same meaning as R^{13}, but is selected independently thereof;

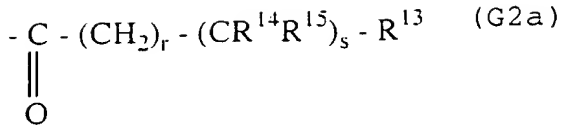
R^{15} is selected from the group consisting of hydrogen, hydroxy, methyl, benzyl, and phenyl,

monocyclic aromatic five or six-member heterocycles, which contain one to three hetero-atoms selected from the group consisting of N, S and O and wherein the heterocycles are either bound directly or over a methylene group,

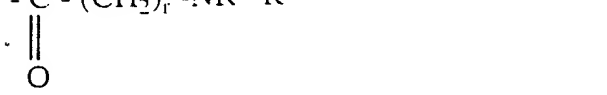
anellated bi- and tricyclic aromatic or partially hydrogenated carbocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein the linkage occurs either over an aromatic or a hydrogenated ring and either directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated heterocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein one to three ring atoms are selected from the group consisting of N, S and O and the linkage occurs either over an aromatic ring or a hydrogenated ring and either directly or over a methylene group,

G^2 is selected from the group consisting of



(G2a)

and 

(G2b)

wherein r, s and the substitutents R^{13} to R^{15} can have the above meaning, or the group $-NR^{13}R^{15}$ is a nitrogen containing heterocycle,

wherein $-NR^{13}R^{15}$ is a nitrogen-containing heterocycle bound over the nitrogen atom selected from the group consisting of

saturated or unsaturated monocyclic, four to eight-membered nitrogen-containing heterocycles,

saturated or unsaturated monocyclic, four to eight-membered nitrogen-containing heterocycles which, aside from the essential nitrogen atom, contain one or two further hetero-atoms selected from the group consisting of N, S and O,

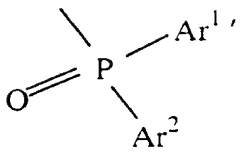
saturated or unsaturated bi- or tricyclic anellated or bridged nitrogen-containing heterocycles with 8 to 16 ring atoms,

saturated or unsaturated bi- or tricyclic anellated or bridged nitrogen-containing heterocycles with 8 to 16 ring atoms which aside from the essential nitrogen atom, contain one or two further hetro-atoms that are selected from N, S and O;

G^3 is $-SO_2-(CH_2)_r-R^{13}$

wherein r and R^{13} have the above meanings,

G^4 is



wherein

Ar^1 and Ar^2 are selected independently from each other from the group consisting of phenyl, pyridyl and naphthyl,

G^5 is $-COR^{16}$

R^{16} is selected from the group consisting of trifluoromethyl, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, and benzyloxy,

wherein G is not $-(CH_2)_r-(CR^{14}R^{15})_s-R^{13}$ [(G1)] when

R^{13} represents pyridyl or phenyl, which may be substituted by halogen, alkyl, alkoxy or trifluoromethyl,

R^{14} represents hydrogen or phenyl, which may be substituted by halogen, alkyl, alkoxy or trifluoromethyl,

R^{15} represents hydrogen,

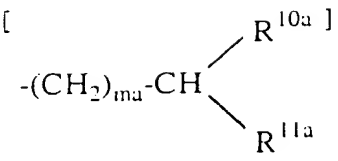
A represents alkylene, substituted ethenylene or butadienylene,

D represents alkylene or alkenylene,

E represents piperazine or homopiperazine, and

s is 1;

wherein G is not <u>phenyl, N-containing heteroaryl or $-(CH_2)_{ma}-CHR^{10a11a}$, wherein:</u>



[phenyl, and N-containing heteroaryl when:] R^{10a} is hydrogen or phenyl, R^{11a} is a phenyl or a pyridyl, and ma is an integer of 0 to 2, and wherein the phenyl group or moiety may be substituted by one or two members selected from the group consisting of halogen, a C_1-C_6 alkyl, trifluoromethyl and a C_1-C_6 alkoxy; when

R^1 is hydrogen, a halogen, a C_1-C_6-alkyl, a C_1-C_6-alkoxy, a C_1-C_6-alkylthio, a C_3-C_8-cycloalkyloxy, a C_3-C_8-cycloalkylthio, a C_2-C_7-alkoxycarbonyl, carboxy, a phenyl, a phenoxy, a phenylthio, 3-pyridyloxy or 3-pyridylthio;

R^2 is hydrogen, a hydroxy, a C_1-C_7-alkanoyloxy or a C_2-C_7-alkoxycarbonyloxy, or when R^1 and R_2 are adjacent to each other, they may combine to form tetramethylene or $-CH_2OCR^{8a}R^{9a}O-$, wherein R^{8a} and R^{9a} are the same or different and are each a C_1-C_6-alkyl;

R^3 is hydrogen, a C_1-C_6-alkyl or a hydroxy-C_1-C_6-alkyl;

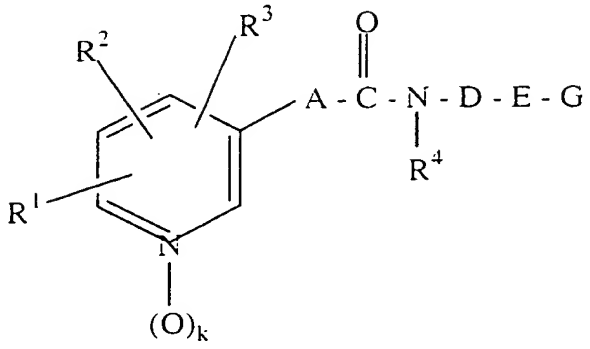
A is a C_1-C_6-alkylene or $-(CR^{6a}=CR^{7a})ra-$, wherein R^{6a} is hydrogen, a C_1-C_6-alkyl or a phenyl, R^{7a} is hydrogen, a C_1-C_6-alkyl, cyano or a phenyl, and ra is 1 or 2;

R^4 is hydrogen;

D is a C_1-C_{10}-alkylene or a C_4-C_{10}-alkylene interrupted by at least one double bond; and

E is selected from the group consisting of piperazine, piperazine, which is substituted by C_1-C_6-alkyl, homopiperazine, and homopiperazine, which is substituted by C_1-C_6-alkyl.

3. (Once amended) A compound according to formula (I)



(I)

wherein

R^1 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, C_3-C_8-cycloalkyl, C_1-C_5-hydroxyalkyl, hydroxy, C_1-C_4-alkoxy, benzyloxy, C_1-C_4-alkylthio, C_1-C_5-alkanoyloxy, C_1-C_4-alkylthio, C_2-C_5-alkoxycarbonyl, aminocarbonyl, C_2-C_5-alkylaminocarbonyl, C_3-C_9-dialkylaminocarbonyl, carboxy, phenyl, phenoxy, phenylthio, pyridyloxy, and NR^5R^6, wherein

R^5 and R^6 are selected independently of each other from hydrogen and C_1-C_6-alkyl;

R^2 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, hydroxy, and C_1-C_4-alkoxy;

R^3 is selected from the group consisting of hydrogen, halogen and C_1-C_6-alkyl;

R^i is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-cycloalkyl, hydroxy, C_1-C_6-alkoxy and benzyloxy;

k is 0 or 1,

A is selected from the group consisting of C_1-C_6-alkylene,

a substituted C_1-C_6-alkylene which is substituted one to three-fold by C_1-C_3-alkyl, hydroxy, fluorine, or phenyl,

C_2-C_6-alkylene, in which a methylene unit is isosterically replaced by O, S, NR^9, CO, SO or SO_2, wherein, with the exception of CO, the isosteric substitution is not adjacent to the amide group and, the residue R^9, is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_1-C_6-acyl and methane sulfonyl;

1,2-cyclopropylene,

C_2-C_6-alkenylene,

a substituted C_2-C_6-alkenylene which is substituted once to three-fold by C_1-C_3-alkyl, hydroxy, fluorine, cyano or phenyl,

C_4-C_6-alkadienylene,

a substituted C_4-C_6-alkadienylene which is substituted once to twice by C_1-C_3-alkyl, fluorine, cyano or phenyl;

1,3,5-hexatrienylene,

a substituted 1,3,5-hexatrienylene which is substituted by C_1-C_3-alkyl, fluorine, cyano, and

ethinylene,

D is selected from the group consisting of C_2-C_{10}-alkylene,

a substituted C_2-C_{10}-alkylene which is substituted once or twice by C_1-C_3-alkyl or hydroxy;

C_4-C_{10}-alkenylene,

a substituted C_4-C_{10}-alkenylene which is substituted once or twice by C_1-C_3-alkyl or hydroxy;

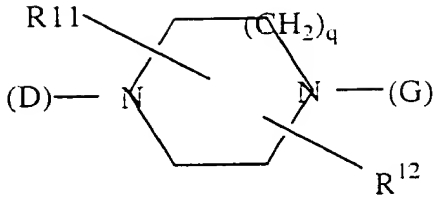
C_4-C_{10}-alkinylene,

a substituted C_4-C_{10}-alkinylene which is substituted once or twice by C_1-C_3-alkyl or hydroxy; and

C_2-C_{10}-alkylene, C_4-C_{10}-alkenylene or C_4-C_{10}-alkinylene, wherein one to three methylene units are isosterically replaced by O, S, NR^{10}, CO, SO, or SO_2, wherein

R^{10} has the same meaning as R^9, but is selected independently thereof;

E is



wherein

q is 1, 2, or 3;

R^{11} is selected from the group consisting of hydrogen C_1-C_3-alkyl, hydroxy, hydroxymethyl, carboxy, and C_2-C_7-alkoxycarbonyl and

R^{12} is selected from the group consisting of hydrogen, and an oxo group adjacent to a nitrogen atom,

and wherein R^{11} and R^{12} may together form a C_1-C_3-alkylene bridge under formation of a bicyclic ring system;

G is selected from the group consisting of G1, G2, G3, G4, and G5, wherein

G^1 is $-(CH_2)_r-(CR^{14}R^{15})_s-R^{13}$

r is 0, 1 or 2,

s is 0 or 1,

R^{13} is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_3-C_8-cycloalkyl; benzyl, phenyl;

monocyclic aromatic five or six-membered heterocycles, which contain one to three hetero-atoms selected from the group consisting of N, S and O, wherein the heterocycles are either bound directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated carbocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein the linkage occurs either over an aromatic or a hydrogenated ring and either directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated heterocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein one to three ring atoms are selected from the group consisting of N, S and O, wherein the linkage occurs either over an aromatic ring or a hydrogenated ring and either directly or over a methylene group,

R^{14} has the same meaning as R^{13}, but is selected independently thereof;

R^{15} is selected from the group consisting of hydrogen, hydroxy, methyl, benzyl, phenyl,

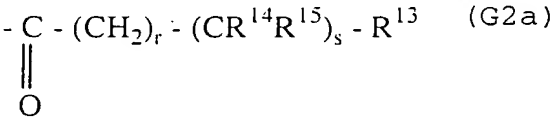
monocyclic aromatic five or six-membered heterocycles, which contain one to three hetero-atoms selected from the group consisting of N, S and O, wherein the heterocycles are either bound directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated carbocyclic ring systems with 8 to 16 ring atoms

and at least one aromatic ring, wherein the linkage occurs either over an aromatic or a hydrogented ring and either directly or over a methylene group, and

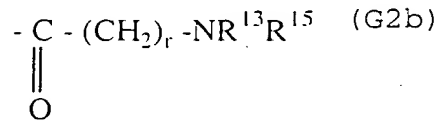
anellated bi- and tricyclic aromatic or partially hydrogenated heterocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein one to three ring atoms can be selected from N, S and O and the linkage may occur either over an aromatic ring or a hydrogenated ring and either directly or over a methylene group;

G^2 is selected from the group consisting of



(G2a)

and



(G2b)

wherein r, s and the substitutents R^{13} to R^{15} can have the above meaning, or the group $-NR^{13}R^{15}$ is a nitrogen containing heterocycle,

wherein $-NR^{13}R^{15}$ is a nitrogen-containing heterocycle bound over the nitrogen atom, the nitrogen-containing heterocycle selected from the group consisting of

saturated or unsaturated monocyclic, four to eight-membered heterocycles,

saturated or unsaturated monocyclic, four to eight-membered heterocycles which aside from the essential nitrogen

atom, contain one or two further hetero-atoms selected from the group consisting of N, S and O,

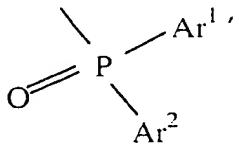
saturated or unsaturated bi- or tricyclic anellated or bridged heterocycles with 8 to 16 ring atoms, and

saturated or unsaturated bi- or tricyclic anellated or bridged heterocycles with 8 to 16 ring atoms that aside from the essential nitrogen atom, contain one or two further hetro-atoms that are selected from the group consisting of N, S and O;

G^3 is $-SO_2-(CH_2)_r-R^{13}$

wherein r and R^{13} have the above meaning,

G^4 is



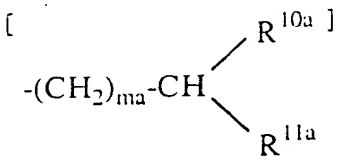
wherein

Ar^1 and Ar^2 are be selected independently from each other from the group consisting of phenyl, pyridyl and naphthyl,

G^5 is $-COR^{16}$

R^{16} is selected from the group consisting of trifluoromethyl, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, and benzyloxy,

wherein G is not phenyl, N-containing heteroaryl or $-(CH_2)_{ma}-CHR^{10a}R^{11a}$, wherein:



[phenyl, and N-containing heteroaryl when:] R^{10a} is hydrogen or phenyl, R^{11a} is a phenyl or a pyridyl, and ma is an integer of 0 to 2, and wherein the phenyl group or moiety may be substituted by one or two members selected from the group consisting of halogen, a C_1-C_6 alkyl, trifluoromethyl and a C_1-C_6 alkoxy; when

R^1 is hydrogen, a halogen, a C_1-C_6-alkyl, a C_1-C_6-alkoxy, a C_1-C_6-alkylthio, a C_3-C_8-cycloalkyloxy, a C_3-C_8-cycloalkylthio, a C_2-C_7-alkoxycarbonyl, carboxy, a phenyl, a phenoxy, a phenylthio, 3-pyridyloxy or 3-pyridylthio;

R^2 is hydrogen, a hydroxy, a C_1-C_7-alkanoyloxy or a C_2-C_7-alkoxycarbonyloxy, or when R^1 and R_2 are adjacent to each other, they may combine to form tetramethylene or $-CH_2OCR^{8a}R^{9a}O-$, wherein R^{8a} and R^{9a} are the same or different and are each a C_1-C_6-alkyl;

R^3 is hydrogen, a C_1-C_6-alkyl or a hydroxy-C_1-C_6-alkyl;

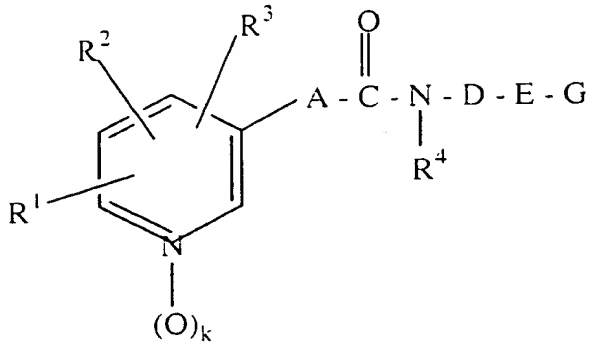
A is a C_1-C_6-alkylene or $-(CR^{6a}=CR^{7a})ra-$, wherein R^{6a} is hydrogen, a C_1-C_6-alkyl or a phenyl, R^{7a} is hydrogen, a C_1-C_6-alkyl, cyano or a phenyl, and ra is 1 or 2;

R^4 is hydrogen;

D is a C_1-C_{10}-alkylene or a C_4-C_{10}-alkylene interrupted by at least one double bond; and

E is selected from the group consisting of piperazine, piperazine, which is substituted by C_1-C_6-alkyl, homopiperazine, and homopiperazine, which is substituted by C_1-C_6-alkyl.

12. (three times amended) A pharmaceutical composition comprising the compound of formula (I)



(I)

wherein:

R^1 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_2-C_6-alkinyl, trifluoromethyl, C_3-C_8-cycloalkyl, C_1-C_6-hydroxyalkyl, hydroxy, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkinyloxy, benzyloxy, C_1-C_7-alkanoyloxy, C_2-C_7-alkoxycarbonyloxy, C_1-C_6-alkylthio, C_3-C_6-alkenylthio, C_3-C_6-alkinylthio, C_3-C_8-cycloalkyloxy, C_3-C_8-cycloalkylthio, C_2-C_7-alkoxycarbonyl, aminocarbonyl, C_2-C_7-alkylaminocarbonyl, C_3-C_{13}-dialkylaminocarbonyl, carboxy, phenyl, phenoxy, phenylthio, pyridyloxy, pyridylthio, and NR^5R^6, wherein

R^5 and R^5 are selected independently of each other from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, benzyl and phenyl;

R^2 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, hydroxy, C_1-C_6-alkoxy, benzyloxy and C_1-C_7-alkanoyloxy;

R^3 is selected from the group consisting of hydrogen, halogen, C_1-C_6-alkyl, trifluoromethyl and C_1-C_5-hydroxyalkyl;

R^4 is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_3-C_6-cycloalkyl, hydroxy, C_1-C_6-alkoxy and benzyloxy;

k is 0 or 1,

A is selected from the group consisting of

C_1-C_6-alkylene,

a susbstituted C_1-C_6-alkylene which is substituted one to three-fold by C_1-C_3-alkyl, hydroxy, C_1-C_3-alkoxy, fluorine, or phenyl,

C_2-C_6-alkylene, in which a methylene unit is isosterically replaced by O, S, NR^9, CO, SO or SO_2, wherein, with the exception of CO, the isosteric substitution is not adjacent to the amide group and R^9 is selected from the group consisting of hydrogen, C_1-C_5-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_1-C_6-acyl and C_1-C_6-alkanesulfonyl,

1,2-cyclopropylene,

C_2-C_6-alkenylene,

a substituted C_2-C_6-alkenylene which is substituted once to three-fold by C_1-C_3-alkyl, hydroxy, C_1-C_3-alkoxy, fluorine, cyano or phenyl,

C_4-C_6-alkadienylene,

a substituted C_4-C_6-alkadienylene which is substituted once or twice by C_1-C_3-alkyl, fluorine, cyano or phenyl;

1,3,5-hexatrienylene,

a 1,3,5-hexatrienylene which is substituted by C_1-C_3-alkyl, fluorine, cyano or phenyl, and

ethinylene,

D is selected from the group consisting of C_2-C_{10}-alkylene,

a substituted C_2-C_{10}-alkylene which is substituted once or twice by C_1-C_6-alkyl, hydroxy, or C_1-C_6-alkoxy;

C_4-C_{10}-alkenylene,

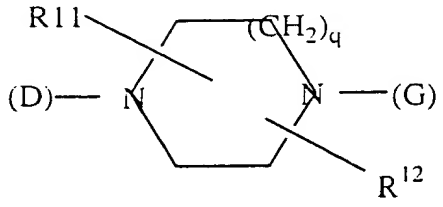
a substituted C_4-C_{10}-alkenylene which is substituted once or twice by C_1-C_6-alkyl, hydroxy, or C_1-C_6-alkoxy;

C_4-C_{10}-alkinylene,

a substituted C_4-C_{10}-alkinylene which is substituted once or twice by C_1-C_6-alkyl, hydroxy, or C_1-C_6-alkoxy; and

C_2-C_{10}-alkylene, C_4-C_{10}-alkenylene or C_4-C_{10}-alkinylene, in which one to three methylene units are isosterically replaced by O, S, NR^{10}, CO, SO, or SO_2, wherein R^{10} has the same meaning as R^9, but is selected independently thereof;

E is



wherein

q is 1, 2, or 3;

R^{11} is selected from the group consisting of hydrogen C_1-C_6-alkyl, hydroxy, hydroxymethyl, carboxy, or C_2-C_7-alkoxycarbonyl,

R^{12} is selected from the group consisting of hydrogen, C_1-C_6-alkyl and an oxo group adjacent to a nitrogen atom,

G is selected from the group consisting of G1, G2, G3, G4, and G5, wherein

G^1 is $-(CH_2)_r-(CR^{14}R^{15})_s-R^{13}$

r is 0 to 3,

s is 0 or 1,

R^{13} is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_3-C_8-cycloalkyl,

saturated or unsaturated four to eight-membered heterocycles,

saturated or unsaturated four to eight-membered heterocycles which contain one or two hetero-atoms selected from the group consisting of N, S and 0,

benzyl, phenyl,

monocyclic aromatic five or six-membered heterocycles,

monocyclic aromatic five or six-membered heterocycles which contain one to three hetero-atoms selected from the group consisting of N, S and O where the heter-atoms and are either bound directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated carbocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein the linkage occurs either over an aromatic or a hydrogenated ring and either directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated heterocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein one to three ring atoms are selected from the group consisting of N, S and O and the linkage can occur either over an aromatic ring or a hydrated ring and either directly or over a methylene group,

R^{14} has the same meaning as R^{13}, but is selected independently thereof;

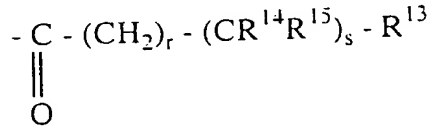
R^{15} is selected from the group consisting of hydrogen, hydroxy, methyl, benzyl, and phenyl,

monocyclic aromatic five or six-member heterocycles, which contain one to three hetero-atoms selected from the group consisting of N, S and O and wherein the hetero-atoms are either bound directly or over a methylene group,

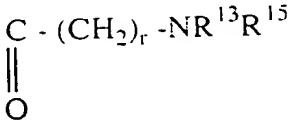
anellated bi- and tricyclic aromatic or partially hydrogenated carbocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein the linkage occurs either over an aromatic or a hydrogenated ring and either directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated heterocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein one to three ring atoms are selected from the group consisting of N, S and O and the linkage occurs either over an aromatic ring or a hydrated ring and either directly or over a methylene group,

G^2 is selected from the group consisting of



and



wherein r, s and the substitutents R^{13} to R^{15} can have the above meaning, or the group $-NR^{13}R^{15}$,

wherein $-NR^{13}R^{15}$ is a nitrogen-containing heterocycle bound over the nitrogen atom selected from the group consisting of

saturated or unsaturated monocyclic, four to eight-membered nitrogen-containing heterocycles,

saturated or unsaturated monocyclic, four to eight-membered nitrogen-containing heterocycles which, aside from the essential nitrogen atom, contain one or two further hetero-atoms selected from the group consisting of N, S and O,

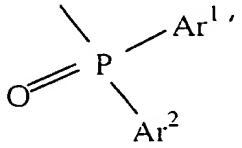
saturated or unsaturated bi- or tricyclic anellated or bridged nitrogen-containing heterocycles with 8 to 16 ring atoms,

saturated or unsaturated bi- or tricyclic anellated or bridged nitrogen-containing heterocycles with 8 to 16 ring atoms which aside from the essential nitrogen atom, contain one or two further hetro-atoms that are selected from N, S and O;

G^3 is $-SO_2-(CH_2)_r-R^{13}$ (G3)

wherein r and R^{13} have the above meanings,

G^4 is



wherein

Ar^1 and Ar^2 are selected independently from each other from phenyl, pyridyl or naphthyl,

G^5 is $-COR^{16}$ (G5)

R^{16} is selected from the group consisting of trifluoromethyl, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, and benzyloxy,

wherein G is not $-(CH_2)_r-(CR^{14}R^{15})_s-R^{13}$ [(G1)] when

R^{13} represents pyridyl or phenyl, substituted by halogen, alkyl, alkoxy or trifluoromethyl,

R^{14} represents hydrogen or phenyl, substituted by halogen,alkyl, alkoxy or trifluoromethyl,

R^{15} represents hydrogen,

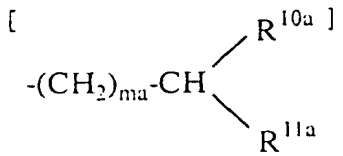
A represents alkylene, substituted ethenylene or butadienylene,

D represents alkylene or alkenylene,

E represents piperazine or homopiperazine, and

S is 1;

[G] <u>wherein G^1</u> is not <u>phenyl, N-containing heteroaryl or $(-CH_2)_{ma}-CHR^{10a}R^{11a}$, wherein:</u>



[phenyl, and N-containing heteroaryl when:] R^{10a} is hydrogen or phenyl, R^{11a} is a phenyl or a pyridyl, and ma is an integer of 0 to 2, and wherein the phenyl group or moiety may be substituted by one or two members selected from the group consisting of halogen, a C_1-C_6 alkyl, trifluoromethyl and a C_1-C_6 alkoxy; when

R^1 is hydrogen, a halogen, a C_1-C_6-alkyl, a C_1-C_6-alkoxy, a C_1-C_6-alkylthio, a C_3-C_8-cycloalkyloxy, a C_3-C_8-cycloalkylthio, a C_2-C_7-alkoxycarbonyl,carboxy, a phenyl, a phenoxy, a phenylthio, 3-pyridyloxy or 3-pyridylthio;

R^2 is hydrogen, a hydroxy, a C_1-C_7-alkanoyloxy or a C_2-C_7-alkoxycarbonyloxy, or when R^1 and R_2 are adjacent to each other, they may combine to form tetramethylene or $-CH_2OCR^{8a}R^{9a}O-$, wherein R^{8a} and R^{9a} are the same or different and are each a C_1-C_6-alkyl;

R^3 is hydrogen, a C_1-C_6-alkyl or a hydroxy-C_1-C_6-alkyl;

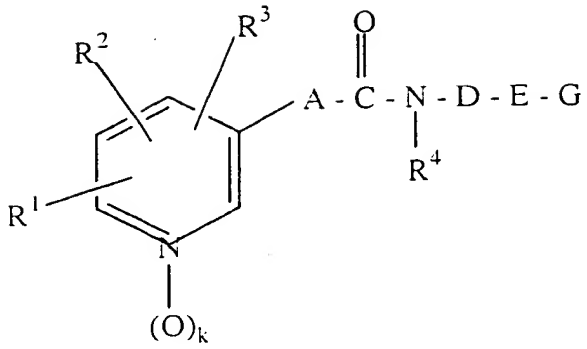
A is a C_1-C_6-alkylene or $-(CR^{6a}=CR^{7a})ra-$, wherein R^{6a} is hydrogen, a C_1-C_6-alkyl or a phenyl, R^{7a} is hydrogen, a C_1-C_6-alkyl, cyano or a phenyl, and ra is 1 or 2;

R^4 is hydrogen;

D is a C_1-C_{10}-alkylene or a C_4-C_{10}-alkylene interrupted by at least one double bond; and

E is selected from the group consisting of piperazine, piperazine, which is substituted by C_1-C_6-alkyl, homopiperazine, and homopiperazine, which is substituted by C_1-C_6-alkyl.

32. (once amended) A pharmaceutical composition comprising the compound of formula (I)



(I)

wherein

R^1 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, C_3-C_8-cycloalkyl, C_1-C_6-hydroxyalkyl, hydroxy, C_1-C_4-alkoxy, benzyloxy, C_1-C_4-alkylthio, C_1-C_5-alkanoyloxy, C_1-C_4-alkylthio, C_2-C_5-alkoxycarbonyl, aminocarbonyl, C_2-C_5-alkylaminocarbonyl, C_3-C_9-dialkylaminocarbonyl, carboxy, phenyl, phenoxy, phenylthio, pyridyloxy, and NR^5R^6, wherein

R^5 and R^6 are selected independently of each other from hydrogen and C_1-C_6-alkyl;

R^2 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, hydroxy, and C_1-C_4-alkoxy;

R^3 is selected from the group consisting of hydrogen, halogen and C_1-C_6-alkyl;

R^4 is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-cycloalkyl, hydroxy, C_1-C_6-alkoxy and benzyloxy;

k is 0 or 1,

A is selected from the group consisting of C_1-C_6-alkylene,

a substituted C_1-C_6-alkylene which is substituted one to three-fold by C_1-C_3-alkyl, hydroxy, fluorine, or phenyl,

C_2-C_6-alkylene, in which a methylene unit is isosterically replaced by O, S, NR^9, CO, SO or SO_2, wherein, with the exception of CO, the isosteric substitution is not adjacent to the amide group and, the residue R^9, is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_1-C_6-acyl and methane sulfonyl;

1,2-cyclopropylene,

C_2-C_6-alkenylene,

a substituted C_2-C_6-alkenylene which is substituted once to three-fold by C_1-C_3-alkyl, hydroxy, fluorine, cyano or phenyl,

C_4-C_6-alkadienylene,

a substituted C_4-C_6-alkadienylene which is substituted once to twice by C_1-C_3-alkyl, fluorine, cyano or phenyl;

1,3,5-hexatrienylene,

a substituted 1,3,5-hexatrienylene which is substituted by C_1-C_3-alkyl, fluorine, cyano, and

ethinylene,

D is selected from the group consisting of C_2-C_{10}-alkylene,

a substituted C_2-C_{10}-alkylene which is substituted once or twice by C_1-C_3-alkyl or hydroxy;

C_4-C_{10}-alkenylene,

a substituted C_4-C_{10}-alkenylene which is substituted once or twice by C_1-C_3-alkyl or hydroxy;

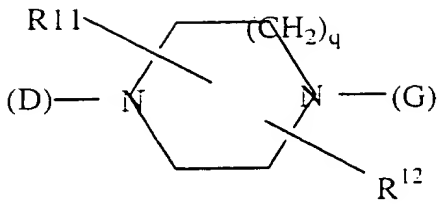
C_4-C_{10}-alkinylene,

a substituted C_4-C_{10}-alkinylene which is substituted once or twice by C_1-C_3-alkyl or hydroxy; and

C_2-C_{10}-alkylene, C_4-C_{10}-alkenylene or C_4-C_{10}-alkinylene, wherein one to three methylene units are isosterically replaced by O, S, NR^{10}, CO, SO, or SO_2, wherein

R^{10} has the same meaning as R^9, but is selected independently thereof;

E is



wherein

q is 1, 2, or 3;

R^{11} is selected from the group consisting of hydrogen C_1-C_3-alkyl, hydroxy, hydroxymethyl, carboxy, and C_2-C_7-alkoxycarbonyl and

R^{12} is selected from the group consisting of hydrogen, and an oxo group adjacent to a nitrogen atom,

and wherein R^{11} and R^{12} may together form a C_1-C_3-alkylene bridge under formation of a bicyclic ring system;

G is selected from the group consisting of G1, G2, G3, G4, and G5, wherein

G^1 is $-(CH_2)_r-(CR^{14}R^{15})_s-R^{13}$

r is 0, 1 or 2,

s is 0 or 1,

R^{13} is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_3-C_8-cycloalkyl; benzyl, phenyl;

monocyclic aromatic five or six-membered heterocycles, which contain one to three hetero-atoms selected from the group consisting of N, S and O, wherein the heterocycles are either bound directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated carbocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein the linkage occurs either over an aromatic or a hydrogenated ring and either directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated heterocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein one to three ring atoms are selected from the group consisting of N, S and O, wherein the linkage occurs either over an aromatic ring or a hydrogenated ring and either directly or over a methylene group,

R^{14} has the same meaning as R^{13}, but is selected independently thereof;

R^{15} is selected from the group consisting of hydrogen, hydroxy, methyl, benzyl, phenyl,

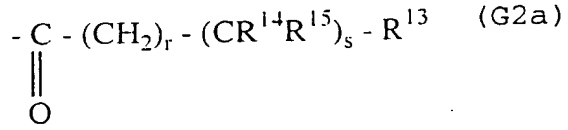
monocyclic aromatic five or six-membered heterocycles, which contain one to three hetero-atoms selected from the group consisting of N, S and O, wherein the heterocycles are either bound directly or over a methylene group,

anellated bi- and tricyclic aromatic or partially hydrogenated carbocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein the linkage occurs

either over an aromatic or a hydrogented ring and either directly or over a methylene group, and

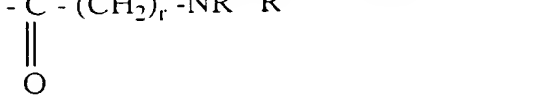
anellated bi- and tricyclic aromatic or partially hydrogenated heterocyclic ring systems with 8 to 16 ring atoms and at least one aromatic ring, wherein one to three ring atoms can be selected from N, S and O and the linkage may occur either over an aromatic ring or a hydrogenated ring and either directly or over a methylene group;

G^2 is selected from the group consisting of



(G2a)

and



(G2b)

wherein r, s and the substitutents R^{13} to R^{15} can have the above meaning, or the group $-NR^{13}R^{15}$ is a nitrogen containing heterocycle,

wherein $-NR^{13}R^{15}$ is a nitrogen-containing heterocycle bound over the nitrogen atom, the nitrogen-containing heterocycle selected from the group consisting of

saturated or unsaturated monocyclic, four to eight-membered heterocycles,

saturated or unsaturated monocyclic, four to eight-membered heterocycles which aside from the essential nitrogen

atom contain one or two further hetero-atoms selected from the group consisting of N, S and O,

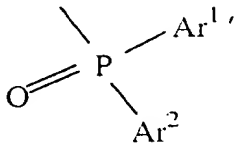
saturated or unsaturated bi- or tricyclic anellated or bridged heterocycles with 8 to 16 ring atoms, and

saturated or unsaturated bi- or tricyclic anellated or bridged heterocycles with 8 to 16 ring atoms that aside from the essential nitrogen atom, contain one or two further hetro-atoms that are selected from the group consisting of N, S and O;

G^3 is $-SO_2-(CH_2)_r-R^{13}$

wherein r and R^{13} have the above meaning,

G^4 is



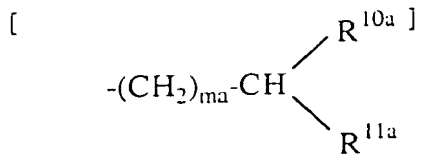
wherein

Ar^1 and Ar^2 are be selected independently from each other from the group consisting of phenyl, pyridyl and naphthyl,

G^5 is $-COR^{16}$

R^{16} is selected from the group consisting of trifluoromethyl, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, and benzyloxy,

wherein G is not phenyl, N-containing heteroaryl or $(-CH_2)_{ma}-CHR^{10a}R^{11a}$, wherein:



[phenyl, and N-containing heteroaryl when:] R^{10a} is hydrogen or phenyl, R^{11a} is a phenyl or a pyridyl, and ma is an integer of 0 to 2, and wherein the phenyl group or moiety may be substituted by one or two members selected from the group consisting of halogen, a C_1-C_6 alkyl, trifluoromethyl and a C_1-C_6 alkoxy; when

R^1 is hydrogen, a halogen, a C_1-C_6-alkyl, a C_1-C_6-alkoxy, a C_1-C_6-alkylthio, a C_3-C_8-cycloalkyloxy, a C_3-C_8-cycloalkylthio, a C_2-C_7-alkoxycarbonyl, carboxy, a phenyl, a phenoxy, a phenylthio, 3-pyridyloxy or 3-pyridylthio;

R^2 is hydrogen, a hydroxy, a C_1-C_7-alkanoyloxy or a C_2-C_7-alkoxycarbonyloxy, or when R^1 and R_2 are adjacent to each other, they may combine to form tetramethylene or $-CH_2OCR^{8a}R^{9a}O-$, wherein R^{8a} and R^{9a} are the same or [difference] different and are each a C_1-C_6-alkyl;

R^3 is hydrogen, a C_1-C_6-alkyl or a hydroxy-C_1-C_6-alkyl;

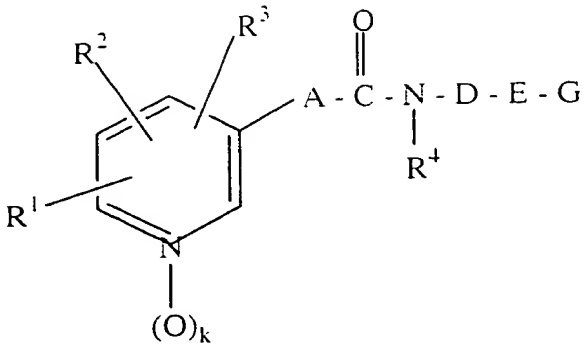
A is a C_1-C_6-alkylene or $-(CR^{6a}=CR^{7a})ra-$, wherein R^{6a} is hydrogen, a C_1-C_6-alkyl or a phenyl, R^{7a} is hydrogen, a C_1-C_6-alkyl, cyano or a phenyl, and ra is 1 or 2;

R^4 is hydrogen;

D is a C_1-C_{10}-alkylene or a C_4-C_{10}-alkylene interrupted by at least one double bond; and

E is selected from the group consisting of piperazine, piperazine, which is substituted by C_1-C_6-alkyl, homopiperazine, and homopiperazine, which is substituted by C_1-C_6-alkyl.

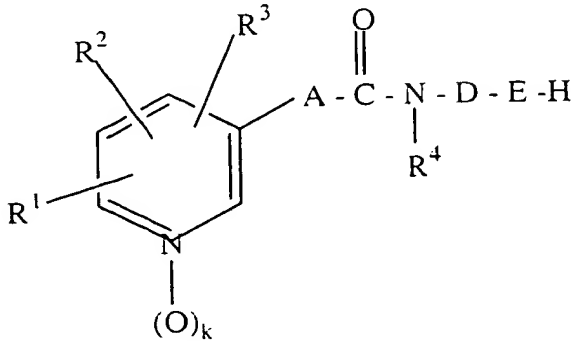
37. (once amended) A method for production of compounds according to formula (I)



(I)

wherein G is selected from the group consisting of an acyl residue, a carbamoyl residue, a sulfonyl residue and a phosphinoyl residue,

wherein compounds of a formula



are reacted with a compound of formula (V)

HO - [X] G (V)

wherein [X] G is selected from the group consisting of acyl residues, carbamoyl residues, sulfonyl residues, phosphinoyl residues, and their reactive derivatives,
wherein:

R^1 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_2-C_6-alkinyl, trifluoromethyl, C_3-C_8-cycloalkyl, C_1-C_6-hydroxyalkyl, hydroxy, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkinyloxy, benzyloxy, C_1-C_7-alkanoyloxy, C_2-C_7-alkoxycarbonyloxy, C_1-C_6-alkylthio, C_3-C_6-alkenylthio, C_3-C_6-alkinylthio, C_3-C_8-cycloalkyloxy, C_3-C_8-cycloalkylthio, C_2-C_7-alkoxycarbonyl, aminocarbonyl, C_2-C_7-alkylaminocarbonyl, C_3-C_{13}-dialkylaminocarbonyl, carboxy, phenyl, phenoxy, phenylthio, pyridyloxy, pyridylthio, and NR^5R^6, wherein

R^5 and R^6 are selected independently of each other from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, benzyl and phenyl;

R^2 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, trifluoromethyl, hydroxy, C_1-C_6-alkoxy, benzyloxy and C_1-C_7-alkanoyloxy;

R^3 is selected from the group consisting of hydrogen, halogen, C_1-C_6-alkyl, trifluoromethyl and C_1-C_6-hydroxyalkyl;

R^4 is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_3-C_6-cycloalkyl, hydroxy, C_1-C_6-alkoxy and benzyloxy;

k is 0 or 1,

A is selected from the group consisting of

C_1-C_6-alkylene,

a susbstituted C_1-C_6-alkylene which is substituted one to three-fold by C_1-C_3-alkyl, hydroxy, C_1-C_3-alkoxy, fluorine, or phenyl,

C_2-C_6-alkylene, in which a methylene unit is isosterically replaced by O, S, NR^9, CO, SO or SO_2, wherein, with the exception of CO, the isosteric substitution is not adjacent to the amide group and R^9 is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkinyl, C_1-C_6-acyl and C_1-C_6-alkanesulfonyl,

1,2-cyclopropylene,

C_2-C_6-alkenylene,

a substituted C_2-C_6-alkenylene which is substituted once to three-fold by C_1-C_3-alkyl, hydroxy, C_1-C_3-alkoxy, fluorine, cyano or phenyl,

C_4-C_6-alkadienylene,

a substituted C_4-C_6-alkadienylene which is substituted once or twice by C_1-C_3-alkyl, fluorine, cyano or phenyl;

1,3,5-hexatrienylene,

a 1,3,5-hexatrienylene which is substituted by C_1-C_3-alkyl, fluorine, cyano or phenyl, and

ethinylene,

D is selected from the group consisting of C_2-C_{10}-alkylene,

a substituted C_2-C_{10}-alkylene which is substituted once or twice by C_1-C_6-alkyl, hydroxy, or C_1-C_6-alkoxy;

C_4-C_{10}-alkenylene,

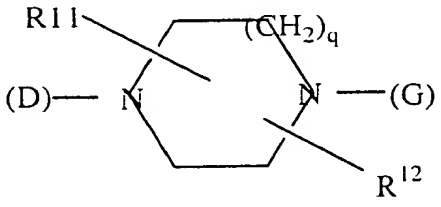
a substituted C_4-C_{10}-alkenylene which is substituted once or twice by C_1-C_6-alkyl, hydroxy, or C_1-C_6-alkoxy;

C_4-C_{10}-alkinylene,

a substituted C_4-C_{10}-alkinylene which is substituted once or twice by C_1-C_6-alkyl, hydroxy, or C_1-C_6-alkoxy; and

C_2-C_{10}-alkylene, C_4-C_{10}-alkenylene or C_4-C_{10}-alkinylene, in which one to three methylene units are isosterically replaced by O, S, NR^{10}, CO, SO, or SO_2, wherein R^{10} has the same meaning as R^9, but is selected independently thereof;

E is



wherein

q is 1, 2, or 3;

R^{11} is selected from the group consisting of hydrogen C_1-C_6-alkyl, hydroxy, hydroxymethyl, carboxy, or C_2-C_7-alkoxycarbonyl,

R^{12} is selected from the group consisting of hydrogen, C_1-C_6-alkyl and an oxo group adjacent to a nitrogen atom.